DETAILED ACTION

The present Office Action is responsive to the Amendment received on April 6, 2011.

Preliminary Remark

Claims 1-16, 19-28, 31-66, 68, and 70 are canceled.

Claims 71 and 72 are new.

Claim Objections

Claim 72 is objected to because of the following informalities: claim 72 contains two commas between the word, "tissue" and the word, "wherein." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The rejection of claims 16 and 28-30 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on February 17, 2011 is withdrawn in view of the Amendment received on April 6, 2011.

Rejections, New Grounds – Necessitated by Amendment

The following rejection is necessitated by Applicants' amendment of broadening the subject matter defined in claim 72 and its dependent claims to a method covering a method pertaining to any cancer involving samples other than breast samples.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 72, 29, 30, and 69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a cancerous or pre-cancerous cell of

the breast, does not reasonably provide enablement for a method of detecting any cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in In Re Wands (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

The Nature of the Invention, Unpredictability of the art, and Enablement Issue:

The nature of the invention relates to a highly unpredictable art of cancer detection based on gene expression and gene copy number determination. It is well known in the art that the development of cancer involves complex, cascades of biochemical reactions. Thus, the enablement issue surround on whether Applicants' discovery of increased copy number, expression levels of a particular gene identified for a particular type of cancer (in the present case, Breast cancer), would enable a skilled artisan to practice the invention for other types of cancers without undue experimentation.

Amount of Guidance and Absence of Working Examples:

The instant specification discloses that Applicants discovered the increased mRNA expression as well as an increased copy number of the gene, "TRIP-13" in breast cancer cell line (page 3, lines 28-32).

The instant specification provides a working example wherein FISH was conducted on breast cancer samples (page 37, lines 25 through page 38).

The instant specification also provides evidence that when amplification status of TRIP13 was examined on formalin-fixed tissue microarray (TMA) containing 785 breast cancer samples by FISH, BAC probe from the TRIP13 region exhibited high-level amplification (>3 fold) in 5% of the total cases (547 samples), low level amplification (2 to 3 fold) in 29% of breast cancer samples (page 39).

While the instant specification provides various working examples for breast cancer and how TRIP13 correlates thereto, the instant specification does not provide any guidance or working examples when it comes to determining/detecting cancers of other origins.

As stated previously, cancer involves multi-factorial processes, involving cascades of biochemical processes. Consequently, a particular gene marker or a trend for said particular gene expression observed for a particular type of cancer do not always equate to its successful usage for determination of other types of cancers.

Such is plainly demonstrated by Knuutila et al. (American Journal of Pathology, 1998, vol. 152, no. 5, pages 1107-1123), wherein Table 1 shows that an increase copy of the gene ABL, is found in a particular type of cancer, Chronic myeloid leukemia. Similarly, the gene HSTF1, is found to be increased in breast cancer and esophegeal carcinoma and so on.

Therefore, it is completely unpredictable as to whether a cancer gene marker found strictly from a single type of cancer could be used for determining other types of cancers.

As set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicants' statement regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> "As we have explained, we have required a greater measure of proof, and for good reason. ***If mere plausibility were the test for enablement*** under section 112, ***applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success***. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

While one may argue that one of skill in the art could have been capable of determining whether the copy number and expression level of TRIP13 was increased in other types of cancers, this does not account for the unpredictability in the art for correlating gene markers as cancer markers, as shown above. Such argument would be what the court considered as, "little more than respectable guesses as to the likelihood of ... success," which would not be a proper showing of enablement.

Therefore, for the above reasons, one of skill in the art would not be capable of practicing the invention fully commensurate in scope of the claims without undue experimentation.

Examiner's Comment

Instantly claimed nucleic acid of SEQ ID NO: 1 is disclosed as encoding the protein of SEQ ID NO 7.

According to the instant specification, SEQ ID Number 1 is a cDNA of the gene, TRIP13, which is disclosed as being increased in both gene copy number as well as transcriptionally over-expressed:

> "In accordance with the present invention, a gene, called TRIP13 (Thyroid hormone Receptor Interacting Protein), has been identified that is both amplified and transcriptionally over-expressed in tumor cells but not in otherwise normal tissues." (page 2, line 31 to page 3, line 3)

Baak et al. (WO 02/10436 A2, issued February 7, 2002, of record) disclose a protein which is 100% identical to instant SEQ ID NO: 7, wherein the artisan disclose that this protein is over-expressed in breast cancer samples (see claim 1).

Baak et al., however, do not disclose that the number of gene copies encoding the protein is increased in breast cancer samples.

Sutherland et al. (Acta Oncologica, 1995, vol. 34, no. 5, pages 651-656) evidences that not all genes which are amplified results in increased expression of the gene products:

> "Increased expression of cyclin D1 was the most common alteration in cyclin gene expression noted in these cell lines. This gene was highly expressed in MDA-MB-134, -175, -330, and -453 cells and one of two MCF-7 variants, Compared with the level of mRNA observed in the majority of the breast cancer cell lines and in two strains of normal, non-transformed breast epithelial cells … Cyclin D1 **gene amplification was detected in six cell lines but amplification was not a prerequisite for, and did not always lead to, increased cyclin D1 expression**." (page 654, 2nd column, bottom paragraph).

Therefore, one of ordinary skill in the art would **not have had a reasonable expectation of success** at concluding that the cause of the increased protein level determined by Baak et al. was based on the increased copy number of the gene encoding that protein.

Since there was no reasonable expectation of success, there would also have been no motivation to arrive at the claimed invention based on the disclosure of Baak et al.

Conclusion

Claims 29, 30, 69, and 72 are rejected.

Claim 72 is objected to.

Claims 17, 18, 67, and 71 are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 6:00 a.m. to 2:30 p.m (M-F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent

to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Young J. Kim/
Primary Examiner
Art Unit 1637
6/17/2011

/YJK/